

Irritable Bowel Syndrome: Current and Emerging Treatment Options

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INTRODUCTION

Irritable bowel syndrome (IBS), one of the most prevalent functional gastrointestinal disorders, affects up to 55 million Americans, most of them women.^{1,2} IBS is a chronic disorder characterized by abdominal pain or discomfort associated with altered bowel function for at least three months, according to the Rome III criteria. Patients often experience relapse of symptoms over time. IBS symptoms cannot be explained by structural abnormalities, and IBS pathophysiology, which is thought to be multifactorial, is not well understood.^{2,3}

EPIDEMIOLOGY

The prevalence of IBS is estimated at 10% to 20% in the general population with an incidence of 1% to 2% a year.⁴ Gastroenterologists spend about 25% of their outpatient office time treating IBS. Prevalence in the U.S. appears to decrease slightly with age and is higher in women than men by a 2:1 ratio.³

DISEASE BACKGROUND AND DIAGNOSIS

IBS is diagnosed based solely on symptoms, which include abdominal pain, distention, or discomfort with altered bowel habits, such as a change in stool frequency or form.⁴ Symptoms of IBS often mimic symptoms of inflammatory bowel disease (IBD), which can make it challenging for physicians to distinguish between the two chronic conditions. The pathophysiology of IBS appears to involve disturbances of the brain-gut axis.⁵ Symptoms of IBS are not explained by diagnostic testing for structural abnormalities; experts propose that symptoms are caused by sensory and motor dysfunction, visceral hypersensitivity, psychological factors, neuroimmune mechanisms, autonomic dysfunction, and irregularity of neurotransmitters or chemical mediators.⁵ This proposed pathophysiology is the rationale behind current treatment approaches.

Symptoms of IBS are often recurrent. They can impair a patient's quality of life, and the health care costs involved are high.⁶ Because IBS is diagnosed based on symptoms alone, a clear definition of the condition is very important. To date, two main criteria have been used. The Manning criteria originated in 1978, and in 1992 the Rome criteria were established by an international team. The Rome criteria were most recently revised in 2005.¹ Through the Rome criteria, IBS was defined by consensus as recurrent abdominal pain or discomfort associated with altered defecation with the exclusion of structural abnormalities. Both the Manning and Rome criteria are used by investigators, and many use a combination of both.

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When considering how to define IBS properly, the American College of Gastroenterology (ACG) IBS Task Force¹ states:

IBS is defined by abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months. Individual symptoms have limited accuracy for diagnosing IBS and, therefore, the disorder should be considered as a symptom complex. Although no symptom-based diagnostic criteria have ideal accuracy for diagnosing IBS, traditional criteria, such as Kruis and Manning, perform at least as well as Rome I criteria; the accuracy of Rome II and Rome III criteria has not been evaluated.

Signs and symptoms of IBS vary from patient to patient, but typically involve altered bowel habits, abdominal pain (often chronic), and abdominal distension.⁷ The symptoms (Table 1) are complex, involving gastrointestinal (GI) and extra-intestinal complaints. An important diagnostic recommendation by the Rome III criteria is that patients must have had recurrent abdominal pain or discomfort for at least three days per month during the past three months that is associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in stool frequency
- Onset associated with a change in stool form or appearance
- Supporting symptoms include:
 - Altered stool frequency
 - Altered stool form
 - Altered stool passage (urgency and/or straining)
 - Mucorrhea
 - Abdominal bloating or subjective distention

Table 1 Common IBS Symptoms

- Diarrhea^a
- Constipation^b
- Mixed diarrhea and constipation^c
- Nausea
- Altered bowel habits
- Cramping
- Flatulence
- Mucus in the stool
- Abdominal fullness
- Abdominal pain

^a Predominant symptom for IBS-D (diarrhea is the most common stool)

^b Predominant symptom for IBS-C (constipation is the most common)

^c Predominant symptom for IBS-M (fluctuates between diarrhea and constipation)

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IBS patients are subdivided according to the predominant stool type. Patients are classified as IBS-D if diarrhea is most common, IBS-C if constipation is most common, or IBS-M if stool fluctuates between diarrhea and constipation.

Of importance, patients with IBS may present with “alarm features” such as nocturnal pain, rectal bleeding, iron deficiency, weight loss, anemia, nocturnal symptoms, and a family history of functional or organic diseases (inflammatory bowel disease, colorectal cancer, and celiac sprue).^{1,8} These alarm features do not offer diagnostic differentiation between patients with IBS and patients with other organic diseases. Also, laboratory data do not differentiate diagnoses because such data, including complete blood counts, are typically normal in patients with IBS. Patients who experience alarm features should seek further evaluation, as these atypical symptoms are not compatible with IBS.

Due to emerging evidence about the risks and benefits of new drugs in IBS treatment, the ACG IBS Task Force has critically evaluated research and developed evidence-based recommendations regarding IBS therapy.¹ The recommendations are graded (Table 2) using a formalized system that demonstrates the strength of evidence found in the literature. Each recommendation is classified as Grade 1 (strong) or Grade 2 (weak), and the strength of evidence is classified as Grade A (strong), Grade B (moderate), or Grade C (weak). All recommendations are cross-referenced with supporting evidence on medical therapies used in the treatment of IBS, as well as alternative therapies.

Table 2 American College of Gastroenterology Task Force on IBS Graded Recommendations¹

Grade	Rating
Strength of recommendation	
1	Strong
2	Weak
Quality of evidence	
A	High
B	Moderate
C	Weak

CURRENT MANAGEMENT OF IBS

Diet, Dietary Fiber, Bulking Agents, and Laxatives

Studies reveal that many patients believe food sensitivities exacerbate their IBS symptoms. Researchers have implemented various exclusion diets, including the elimination of dairy, cereals, citrus fruits, potatoes, caffeine, alcohol, additives, and preservatives. However, many of these studies did not include control groups, which makes the results difficult to interpret properly given the high placebo response rate seen in IBS studies. Therefore, the ACG IBS Task Force recommends against food-allergy testing and exclusion diets (Grade 2C recommendation).

The effectiveness of dietary fiber, bulking agents, and laxatives in the management of IBS have all been studied, but many studies had poor designs, short durations, and small sample sizes.

A systematic review of 12 trials comparing fiber with placebo in IBS found modest benefit with psyllium hydrophilic mucilloid but no benefit with bran fibers. Therefore, the ACG IBS Task Force makes weak recommendations (Grade 2C) to support the use of psyllium hydrophilic mucilloid and recommends against routine use of wheat bran or corn bran. However, since the publication of the IBS Task Force Review, the Cochrane Collaboration has published a review on bulking agents for IBS treatment.⁹ Although the review considered many of the same studies, the authors concluded that the evidence does not support a benefit for bulking agents in treating IBS.

Laxative use has not been studied in well-designed trials for IBS. One study with polyethylene glycol 3350 in adolescents with IBS-C showed benefit for stool frequency with no effects on abdominal pain.¹ A recent 28-day trial in adults also demonstrated benefits in stool frequency but failed to improve abdominal discomfort and pain when compared to placebo.¹⁰

Probiotics

The human gastrointestinal tract is a complex system containing a variety of bacterial communities of microflora. Probiotics are defined as “live, micro-organisms, which when consumed in adequate amounts, confer a health effect on the host.”^{11,12} A variety of probiotic strains are found in the gut, and many strains are available commercially. The most common probiotic products contain *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Streptococcus*, and *Leuconostoc* strains.¹¹

Many clinical trials have been conducted regarding the role of probiotic therapy in a variety of disease states. In recent years, probiotics have gained attention for the treatment of IBS. Some studies suggest that patients who use probiotics to help alleviate IBS find modest improvement in overall symptoms after several weeks of treatment.^{11,12} Although many studies have been conducted in this area, the heterogeneity of study designs makes comparisons difficult. Treatment groups in these studies included a variety of probiotic strains. Some studies used one probiotic, while others used multiple strains. The length of treatment and dosage of probiotic also varied. In addition, the results have been mixed; adult patients in some studies reported a statistically significant improvement in abdominal pain, bloating, and flatulence, while others did not.¹² The ACG IBS Task Force recognizes some efficacy (Grade 2C) regarding use of probiotics bifidobacteria and certain probiotic combinations, but evidence does not support the use of lactobacilli alone. Additional well-designed studies are needed in this area.^{1,12}

Antispasmodics

Antispasmodic medications such as hyoscamine and dicyclomine have been used to treat IBS for decades. These medications have antimuscarinic and anticholinergic activities, which result in decreased GI motility and smooth muscle spasms. Because these medications were approved by the FDA many years ago, few well-designed studies support their efficacy, and most purported benefits are based on clinical observations over time. Limited evidence does support efficacy, but most of the evidence is for antispasmodic medications that are not available in the United States;^{1,9} certainly, further studies are needed.

The ACG IBS Task Force gives antispasmodics a Grade 2C

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recommendation for short-term relief of abdominal pain and discomfort, while acknowledging that evidence for safety, tolerability, and long-term efficacy is limited or unavailable.¹ Common adverse events that occur with these medications mostly relate to anticholinergic side effects such as anhidrosis, blurred vision, confusion, constipation, urinary retention, xerostomia, and drowsiness.

Antidepressants

Although neither class of medications has been approved by the FDA for treatment of IBS, both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have been studied in this population. Studies have shown benefit in IBS despite the use of lower doses than often seen in the treatment of depression. A Cochrane review found benefit for IBS patients in abdominal pain, global assessment, and IBS symptom score, with the results varying somewhat with the antidepressant class studied.⁹ In subgroup analyses, SSRIs showed benefit for global assessment while TCAs improved abdominal pain and IBS symptom scores. The ACG IBS Task Force recognizes the efficacy of antidepressants at relieving global IBS symptoms and reducing abdominal pain (Grade 1B).¹ A recent systematic review and meta-analysis of antidepressant use in IBS also recognizes the efficacy of these classes of medications, finding similar treatment effects for both TCAs and SSRIs. There are no long-term studies of antidepressant use in IBS and no head-to-head trials comparing TCAs to SSRIs in IBS patients.¹³

Antidiarrheals

Loperamide (Imodium, McNeil Consumer Healthcare) is the only antidiarrheal that has been sufficiently studied in trials with IBS-D patients,¹ but it is not specifically approved for IBS by the FDA. It acts on the circular and longitudinal muscles, through the opioid receptor, to inhibit peristalsis. The ACG IBS Task Force gives loperamide a 2C recommendation for reducing stool frequency and improving stool consistency because these benefits were shown in two small, randomized, controlled trials. No benefits were seen in reducing abdominal pain or global IBS symptoms, so loperamide cannot be recommended to resolve these problems.

Tegaserod

Tegaserod (Zelnorm, Novartis) is a partial agonist at the serotonin type-4 receptor (5-HT₄), which stimulates the peristaltic reflex and intestinal secretions and decreases visceral sensitivity.¹⁴ It binds to 5-HT₄ receptors with high affinity and has moderate affinity for 5-HT₁ receptors but no appreciable affinity for 5-HT₃ receptors.

Three multicenter, double-blind, placebo-controlled trials were conducted in patients with IBS with constipation prior to FDA approval for tegaserod. Nearly 2,500 women with at least a three-month history of IBS symptoms were enrolled in these trials. IBS symptoms included abdominal pain, bloating, and constipation, with constipation defined as at least two of the following symptoms, each occurring at least 25% of the time: less than three bowel movements per week, hard or lumpy stools, or straining with a bowel movement. Each week of the study, patients were asked to rate overall well-being and

current symptoms of abdominal discomfort, pain, and altered bowel habits compared to usual symptoms prior to study entry. Patients who reported either considerable or complete relief for two or more of the four weeks and patients who reported they were somewhat relieved for all four weeks were considered responders to drug therapy. Studies included 12 weeks of double-blinded treatment. Two studies used a tegaserod dose of 6 mg twice daily and the third study explored tegaserod dose titration.

In study one, 31% of tegaserod patients responded to therapy in month 1, compared with 17% of patients taking placebo. In month 3, 39% of tegaserod patients were responders, compared with 28% of patients taking placebo. These results were statistically significant for both time frames. Study two results were similar initially, with 35% of tegaserod patients and 22% of placebo patients classified as responders in month 1. At month 3, however, 44% of tegaserod patients and 39% of placebo patients were responders; this difference was not statistically significant. Much like study two, in the third study 34% of tegaserod patients and 20% of placebo patients responded to drug therapy in month 1, which was statistically significant, but the statistical significance disappeared in month 3, with 43% responding to tegaserod and 38% responding to placebo.

Almost 300 males were enrolled in two of the trials, but no significant differences were found between tegaserod and placebo when male patients were analyzed as a separate group, which led to FDA approval being restricted to females. Additional labeling restrictions include short-term (12-week) use and constipation as the primary bowel symptom of IBS. Tegaserod has an additional FDA indication for the treatment of chronic idiopathic constipation in patients younger than 65 years of age, based on separate clinical trials.

The ACG IBS Task Force gives tegaserod a Grade 1A recommendation and states that it is more effective than placebo in relieving global IBS symptoms in women with IBS-C.¹ It was also given a Grade 1B recommendation for relief of global IBS symptoms in patients with IBS-M. However, since 2007, tegaserod is only available from the FDA through an emergency investigational new drug protocol due to an elevated risk of cardiovascular events.¹⁵

Alosetron

Alosetron (Lotronex, Prometheus Laboratories) is an antagonist at the 5-HT₃ receptor.¹⁶ Because activation of 5-HT₃ receptors results in neuronal depolarization related to visceral pain, colonic transit, and GI secretions, alosetron modulates an integral part of the enteric nervous system. FDA approval of alosetron is limited to women with severe diarrhea-predominant IBS who have no anatomical or biochemical abnormalities of the GI tract. They must also have chronic IBS symptoms that have not responded to conventional therapy.

FDA approval for alosetron is supported by three 12-week, randomized, double-blind, placebo-controlled trials that enrolled nearly 2,000 women with severe IBS-D as defined by Rome II criteria. Two of the studies enrolled women with IBS-D who had bowel urgency at least 50% of the days. Those receiving alosetron 1 mg twice daily had improvements in days with urgency control, average stool consistency, and average stool frequency. The third trial enrolled women with IBS-D who also

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had frequent and severe abdominal pain or discomfort, frequent bowel urgency or fecal incontinence, or disability or limitation of daily activities due to IBS.¹⁷ Patients were randomized to three doses of alosetron. Patients compared symptoms on a monthly basis to how they felt in the three-month period prior to study entry. Symptoms were rated on a seven-point scale, and patients were considered responders if they reported moderate or substantial improvement. All alosetron treatment groups had more responders at 12 weeks compared with patients receiving placebo. Additionally, treatment with alosetron has shown improvement in quality of life in this patient population.¹⁸

The most common adverse reactions to alosetron include constipation, nausea, abdominal discomfort, and abdominal pain.¹⁶ Patients should discontinue alosetron if they develop constipation due to potential serious complications of constipation, including obstruction, ileus, toxic megacolon, ischemic colitis, and secondary bowel ischemia. Alosetron has a boxed warning for these serious GI adverse events, which have resulted in surgery and death in some patients. To promote communication of these risks and minimize unnecessary exposure to alosetron, patients and prescribers must enroll in a prescribing program before alosetron can be dispensed. This program, along with required distribution of a medication guide with each prescription, is part of a risk evaluation and mitigation strategy (REMS) to limit the risk of serious complications by ensuring that alosetron is used only in severely affected patients for whom the risk–benefit ratio is favorable.

The ACG IBS Task Force recognizes that alosetron is effective in relieving IBS symptoms but at the risk of potential serious side effects.¹ Alosetron is best used in women with severe IBS and diarrhea who have not responded to conventional therapy (Grade 1B).

Lubiprostone

Lubiprostone (Amitiza, Takeda) is a locally acting type-2 chloride channel (ClC-2) activator that activates ClC-2 in the apical membrane of the intestine.¹⁹ This results in increased excretion of chloride ions into the intestinal lumen, which leads to passive transport of sodium and water. Increased intestinal fluid secretion stimulates motility in the intestine. Lubiprostone is approved for women 18 years of age and older at a dose of 8 mcg twice daily. It is also approved for chronic idiopathic constipation in adults when used at a higher dose.

Approval for lubiprostone is based on two similar, randomized, double-blind, placebo-controlled phase 3 trials in adults meeting the criteria for constipation-predominant IBS.²⁰ Patients were assigned to placebo or lubiprostone 8 mcg twice daily for 12 weeks. They recorded spontaneous bowel movements (SBM) and rated symptoms including bowel movement consistency, constipation severity, straining, and abdominal bloating and discomfort. The primary outcome of the studies was responder status, based on self-reported symptoms and relief. Secondary outcomes included ratings of individual symptoms and SBM frequency. A total of 1,171 patients, 91% of them female, were randomized to a treatment group. Significantly, more patients assigned to lubiprostone were categorized as overall responders (17.9% vs. 10.1%), but response rates were low for both groups. During the study, more patients assigned to lubiprostone reported improvement in abdominal discomfort

and pain, abdominal bloating, bowel movement frequency, stool consistency, and straining, but these improvements were significant for only part of the study duration. The most frequently reported adverse events were nausea (8% with lubiprostone and 4% with placebo) and diarrhea (6% with lubiprostone and 4% with placebo).

Among patients completing the phase 3 trials, 522 were enrolled into an extension study, taking lubiprostone for 36 weeks to assess long-term safety and tolerability.²¹ Mild-to-moderate nausea and diarrhea were the most common adverse events, each occurring in 11% of patients. Responder rates increased over time, with up to 44% of patients being classified as responders to lubiprostone. However, this does not include patients who dropped out of the study. Dropouts accounted for 41.8% of the enrolled patients, including 18.1% who dropped out for lack of efficacy. Additionally, there was no placebo comparator group in this extension study. Due to the high dropout rate, the lack of a placebo group, the fact that IBS symptoms can fluctuate, and the realization that there is often a high placebo response rate in IBS studies, these results should be interpreted cautiously.

The ACG IBS Task Force gives lubiprostone a Grade 1B recommendation and states that it is more effective than placebo in relieving global IBS symptoms in women with IBS-C.¹ Due to lubiprostone's safety profile and the potential for symptom relief in this population, it is a reasonable medication to try as long as patients and prescribers evaluate benefits (or lack thereof) after a trial period.

Linacotide

Linacotide (Linzess, Ironwood Pharmaceuticals) is a guanylate cyclase-C (GC-C) agonist that works locally on the luminal surface of the intestinal epithelium. Both intracellular and extracellular levels of cyclic guanosine monophosphate (cGMP) are increased when GC-C is activated. Increased levels of intracellular cGMP result in chloride and bicarbonate secretion into the intestinal lumen, while increased extracellular levels of cGMP decrease the activity of pain-sensing nerves. These actions result in increased intestinal fluid, accelerated transit time, and a reduction in intestinal pain. Linacotide is approved for adults with IBS-C at a dose of 290 mcg once daily and in adults with chronic idiopathic constipation at a dose of 145 mcg once daily.²²

Use of linacotide is contraindicated in pediatric patients through 5 years of age due to death in young juvenile mice during toxicology studies. Although linacotide did not cause death in older juvenile mice, its use should be avoided in any patient under the age of 18 due to lack of safety and efficacy data.²²

FDA approval for linacotide is supported by two similarly designed, randomized, double-blind, placebo-controlled phase 3 trials by Rao²³ and Chey.²⁴ Patients were enrolled if they met modified Rome II criteria for IBS and had a mean score of 3 or more on a 0–10 point scale measuring abdominal pain during the two-week baseline period. Patients also had to average less than three complete spontaneous bowel movements (CSBMs) per week and five or fewer SBMs per week during this baseline period. Patients were assigned to placebo or linacotide 290 mcg once daily. The trials had four primary endpoints. Per FDA guidance,²⁵ efficacy was assessed by a 30% reduction from baseline in mean abdominal pain and an increase of at least

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one CSBM per week from baseline.^{23,24} Individual parameters were assessed weekly, and a patient had to meet the combined endpoint for at least six of the first 12 weeks. The other three primary endpoints were responders who had a 30% reduction in abdominal pain (criteria i), who had three or more CSBMs and at least one more CSBM than at baseline (criteria ii), and who met both criteria i and ii in the same week. For these three endpoints, patients were considered responders if they met the criteria for at least nine of the first 12 weeks.

More than 800 patients, 90% of whom were female, were randomized to treatment with placebo or linaclotide in each trial. In each trial, 33% of patients taking linaclotide met the responder criteria defined by the FDA; 21% and 13.9% of patients taking placebo met the responder criteria in Rao's trial and Chey's trial, respectively. Patients assigned to linaclotide were more likely to be responders for both the individual endpoints and the combined endpoints. Patients began to see improvements in one week, but maximum effects were not seen for several weeks. Rao's trial re-randomized the linaclotide group after 12 weeks of treatment. Those who continued on linaclotide maintained benefits for the additional four weeks studied, but those who were switched to placebo returned to baseline in a week. Diarrhea (mostly mild or moderate) was the most frequently reported adverse event, occurring in nearly 20% of linaclotide patients in each trial. Diarrhea caused treatment discontinuation in approximately 5% of linaclotide patients.

Linaclotide was approved by the FDA after publication of the ACG's evidence-based systemic review, so there are no ACG recommendations for or against its use. Like lubiprostone, it has had low response rates in clinical trials, but strict criteria were used to define responders. Linaclotide hasn't been studied in clinical trials longer than 26 weeks, so long-term safety and efficacy haven't been fully evaluated. However, it is the only medication for IBS-C that is approved in both men and women. Because of its safety and potential for efficacy, linaclotide is an appropriate option in adult patients with IBS-C.

EMERGING TREATMENT OPTIONS

Asimadoline

Asimadoline (Tioga Pharmaceuticals) is a kappa opioid receptor agonist that has been shown to produce both analgesic and antidiarrheal effects. It is being investigated in a phase 3 clinical trial for people with IBS-D. In phase 2 testing, two randomized, double-blind, placebo-controlled trials have been completed. One was a four-week study to evaluate the effect of on-demand treatment with asimadoline in patients with IBS of any subtype.²⁶ The primary outcome measure was severity of abdominal pain two hours after treatment of pain, but asimadoline did not show a benefit in this trial. The other trial was a 12-week dose-ranging study that enrolled nearly 600 patients with any subtype of IBS.²⁷ Three doses of twice-daily asimadoline were compared to placebo. The primary endpoint was the total number of months with adequate relief of IBS pain or discomfort. Although the intent-to-treat patient population did not show a statistically significant benefit, asimadoline appeared to benefit patients with high baseline levels of pain, especially IBS-D patients.

The phase 3 clinical trial was also a randomized, double-blind, placebo-controlled study.²⁸ An estimated 600 patients

with IBS-D were expected to be enrolled and randomized to asimadoline 0.5 mg twice daily or placebo for 12 weeks. Patients were asked to assess symptoms daily and record bowel movements; response to drug therapy was determined weekly. A weekly response to drug therapy was defined as a 30% or greater decrease in baseline IBS-related abdominal pain and a 25% or greater decrease in the average number of daily bowel movements. The primary efficacy endpoint, overall study responders, was defined as patients who were weekly responders at least six of the 12 weeks. Although this study has been completed, results are not yet available.

Eluxadoline

Eluxadoline (Furiex Pharmaceuticals) is a mu-opioid receptor agonist and a delta-opioid receptor antagonist that had beneficial results in a phase 2 study.²⁹ In the study, 807 patients with IBS-D were randomized to receive placebo or one of four doses of eluxadoline for 12 weeks. The primary endpoint was clinical response at week 4, based on daily diary entries for that week. Response was considered a mean pain reduction from baseline of at least 30% and at least 2 points on a 0–10 scale, as well as a stool consistency score of 3 or 4 (range 1–7, Bristol Stool Scale) on at least 66% of diary entries. Compared with placebo, a significantly greater percentage of patients met the study responder definition with eluxadoline at 100 mg twice daily and 200 mg twice daily. The most common adverse events were vomiting, nausea, and abdominal pain. The incidence of abdominal pain and nausea with eluxadoline 100 mg was similar to that of placebo.

Two phase 3 trials of eluxadoline have recently been completed.³⁰ The studies, which randomized 2,428 total patients (two-thirds of whom were female) with IBS-D to take placebo, eluxadoline 75 mg twice daily, or eluxadoline 100 mg twice daily, had the same overall trial design. Patients recorded daily symptoms and stool consistency. The primary outcome was a composite response over 12 or 26 weeks demonstrating improvement in abdominal pain and stool consistency over baseline. A patient had to have improvement in both categories on the same day to be a daily responder. Overall response rates were compared for patients who met these daily response criteria for at least 50% of the days during the 12- or 26-week study period. Statistically significant improvements in responder rates through 12 weeks were seen in each of the studies. The pooled analysis showed response in 16.7% of patients taking placebo, 26.2% of patients taking eluxadoline 75 mg twice daily, and 27% of patients taking eluxadoline 100 mg twice daily. Pooled results showed eluxadoline was also beneficial for the 26-week study duration. Response was evident within days of starting therapy and the results were statistically significant for both males and females. The most common adverse events reported in patients taking eluxadoline were constipation and nausea, with both occurring in less than 10% of patients. Eight patients receiving eluxadoline had hepatobiliary sphincter of Oddi spasm, which most often began in the first week of treatment. All of these patients had a prior cholecystectomy, so further investigation in this patient population seems warranted.

Eluxadoline has been granted fast track status by the FDA and a new drug application is expected to be submitted this year.

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Rifaximin

Rifaximin (Xifaxan, Salix Pharmaceuticals) is a nonabsorbable antibiotic that is FDA-approved for travelers' diarrhea and reduction in risk of hepatic encephalopathy,³¹ but it has also been studied in several well-designed randomized, controlled trials for IBS.³² The two largest trials, TARGET 1 and TARGET 2, were identical in design.³³ Each trial randomized patients with a diagnosis and current symptoms of IBS, such as pain and discomfort, to rifaximin 550 mg or placebo three times a day for 14 days; patients with constipation-predominant IBS were excluded. The primary endpoint was the proportion of patients with adequate relief of global IBS symptoms, with adequate relief defined as self-reported relief of symptoms for at least two of the first four weeks after treatment. More patients in the rifaximin group reported adequate relief of global IBS symptoms (40.7% vs. 31.7% in the two studies combined). During the 10-week follow-up period, improvement over placebo seemed to decline, although it remained statistically significant. Additionally, studies of rifaximin's use in IBS have been short, leaving questions about long-term efficacy and an appropriate course of action if symptom relief relapses.³² The FDA has denied approval of Xifaxin's indication for IBS and has requested evidence that rifaximin is effective with repeat treatment following recurrence of symptoms.³⁴ Salix Pharmaceuticals is recruiting an estimated 800 patients for TARGET 3, a study to evaluate the safety and efficacy of repeat treatment with rifaximin in IBS-D patients who respond to initial treatment with rifaximin.³⁵

In a recent meta-analysis,³² five rifaximin trials (out of 18 manuscripts and abstracts that were reviewed) met the inclusion criteria as randomized, placebo-controlled studies that enrolled patients with defined symptom-based criteria of IBS (Manning, Kruis, Rome I, Rome II, or Rome III). The primary endpoint, reported global improvement in IBS symptoms, was more favorable for rifaximin (42.2%) compared with placebo (32.4%). The number needed to treat (NNT) to see benefit with rifaximin was 10. The secondary outcome of bloating also showed benefit with rifaximin (NNT = 10), but results were mixed regarding improvement in stool consistency and abdominal pain. Because adverse events were minimal and similar to placebo and the modest therapeutic benefit is similar to other medications approved for IBS, this meta-analysis supports use of rifaximin in IBS.

The ACG IBS Task Force supports a short-term course of rifaximin for global improvement of IBS and bloating (Grade 1B), with benefits likely limited to patients with IBS-D or bloating.¹ Long-term safety and efficacy are still unknown, and evidence-based information concerning treatment of recurrent symptoms is lacking, but clinical trials have demonstrated a positive safety profile. The most common adverse events were headache, upper respiratory tract infection, abdominal pain, nausea, diarrhea, and pharyngitis, but the incidence of these events was similar to placebo.^{32,33}

CONCLUSION

IBS is a chronic functional disorder of the gastrointestinal tract with symptoms of abdominal pain and altered bowel habits that include diarrhea, constipation, or both. Patients who suffer from IBS often have an impaired quality of life. IBS affects 10% to

20% of the general population, but these percentages are likely underestimated, since only a small portion of patients with IBS symptoms seek medical attention. Patients who suffer from IBS often do not respond to lifestyle and diet modifications.

Although a few FDA-approved medications are available to treat IBS symptoms, several of these drugs have strict limitations on use. Many patients do not find complete symptomatic relief, even when physicians explore off-label drug options. Well-designed studies are needed to support the use and optimize the dosing for older medications that are used off-label. Additionally, comparative effectiveness studies, which would help guide treatment selection, are lacking for IBS medications. Emerging treatment options for IBS, such as asimadoline, eluxadoline, and rifaximin, show promise, but better understanding of the disease pathophysiology is needed to facilitate drug development.

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